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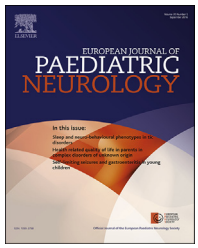

Case Study

Autosomal dominant SCN8A mutation with an unusually mild phenotype

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ABSTRACT

Background: Mutations in SCN8A, coding for the voltage-gated sodium channel Na_v 1.6, have been described in relation to infantile onset epilepsy with developmental delay and cognitive impairment, in particular early onset epileptic encephalopathy (EIEE) type 13.
Case report: Here we report an infant and his father with early onset focal epileptic seizures but without cognitive or neurological impairment in whom next generation sequence analysis identified a heterozygous mutation (c.5630A > G, p. (Asn1877Ser)) in the SCN8A gene. This mutation, confirmed by Sanger sequence analysis, affects a highly conserved amino acid and in silico tools predicts that it may be pathogenic.

The reported infant has a normal developmental profile at 16-month follow-up. His father also had normal development and has no cognitive impairment at 42 years. This is the second known SCN8A mutation associated with a phenotype of benign familial infantile epilepsy. Good seizure control was achieved in our patients with sodium channel blockers.
Conclusion: Based on our proband and a recently described group of families with benign familial infantile epilepsy and SCN8A variant we suggest expanding testing to patients with infantile epilepsy and no cognitive impairment. In addition, the same SCN8A variant (c.5630A > G, p. (Asn1877Ser)) is also found in patients with epilepsy and developmental delay highlighting the phenotypic variability and the possible role of other protective genetic factors.

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1. Introduction

Infantile epilepsy is associated with a growing number of genetic mutations in voltage-gated sodium channels, expressed in the central nervous system.[1–3] These sodium channels are made up of a pore-forming α-subunit and two smaller β-subunits which together regulate neuronal excitability. The gene SCN8A, encodes the sodium channel α-subunit Na_v 1.6, a protein of 1980 residues positioned on chromosome 12q13.[2,3] Pathogenic mutations in the gene SCN8A have been identified in 1% of patients with epileptic encephalopathy.[1] The pathogenesis of epileptic encephalopathy has been predominantly associated with gain-of-function mutations of SCN8A causing increased activation of the Na_v 1.6 sodium channel.[3] This is strengthened by evidence from a mouse model $SCN8A^{N1768D/+}$ in which heterozygous gain-of-function mutation led to onset of seizures at 2–4 months of age and premature death within 1 year of age.[3]

Patients with a pathogenic SCN8A mutation present with epilepsy at an average age of 4 months, and although the seizure semiology is varied, approximately half begin with tonic-clonic seizures and most children develop additional seizure types such as epileptic spasms and absence seizures.[1,2] Typically, patients with epilepsy associated with a SCN8A mutation developed early onset epileptic encephalopathy with cognitive impairment and developmental delay. However, a recent report described three unrelated families with a pathogenic SCN8A mutation (c.4447G > A; p. Glu1483-Lys) associated with a milder phenotype of infantile epilepsy without developmental delay.[4]

In this case report, we describe a family of two cases of early onset epilepsy with no developmental delay and a recurrent SCN8A mutation, previously associated with cases of the more severe early onset epileptic encephalopathy.

2. Case report

2.1. Case 1, the proband

The proband is a white British male now aged 16 months, born by normal vaginal delivery at term following an uneventful pregnancy. He is the second child of an unrelated white British-New Zealander couple. Apart from a history of early onset epilepsy in his father, there was no other significant family history of note.

The patient presented with focal seizures that involved eye deviation to the left with secondary tonic generalization, starting at 5 months of age. Some of these were associated with apnoea. The duration of seizures varied from 30 s to 10 min. General examination showed no facial dysmorphism or other abnormality and the neurological examination was normal. The Brain MRI and neuro-metabolic investigations were also normal. This included normal serum electrolytes, calcium, magnesium, pipecholic acid, uric acid, creatine kinase, ammonia, triglycerides, biotinidase, acyl carnitine, thyroid functions and amino acid profile. Urine organic acid, alpha-aminoadipic semialdehyde and toxicology were also normal. CSF analysis showed normal glucose (2.9 mmol/l), protein (0.18 g/l), lactate (1.3 mmol/l) and amino acid levels.

An initial electroencephalogram (EEG) at 5 ½ months of age was normal.

He was treated with intravenous phenytoin during the acute phase and then commenced on Carbamazepine.

A 48-h ambulatory EEG of the proband at 8 months of age on carbamazepine at approximately 15 mg/kg/day showed a background rhythm that was slow and disorganised for age (Fig. 1A) and a build up of rhythmic fast activity (Fig. 1B).

He has progressed through his developmental milestones normally with head control at 3 months of age and sitting independently at 6 months. Currently, he can stand up, walk unaided and climb stairs. He babbles, can say a few words and has no visual or hearing impairment. Neurological and general examination remains normal at 16-month follow-up. Carbamazepine has controlled seizures at a dose of 30 mg/kg/day.

2.2. Case 2, the proband's father

The proband's father is a 42-year-old New Zealand European male born by normal delivery at term, following an uneventful pregnancy. He too had presented with seizures at 4 months of age, referred to as generalized tonic-clonic seizures and the brain MRI was described as normal. Initially phenytoin was used with good seizure control, and when an attempt was made to stop this at around 12 years of age, his seizures returned. Phenytoin was restarted the same year and continued until his early thirties when it was switched to sodium valproate in view of the better safety profile. Seizures have been controlled well on sodium valproate 1 g twice a day and he has remained seizure free for the last 7 years. Developmental milestones remained completely normal through childhood and he has no learning difficulties. He is a science graduate working as a research scientist.

2.3. Genetic testing

The proband underwent genetic testing using a 66-gene panel (Appendix 1) due to the unexplained early onset of seizures. Array CGH (comparative genomic hybridisation) was also performed and was normal. Genomic coordinates of 66 genes known to cause one or more epileptic encephalopathy syndromes were uploaded to Agilents SureDesign Tool (https://earray.chem.agilent.com/suredesign/) to create the targeted panel. Libraries were made following the SureSelectXT custom capture protocol (Agilent Technologies) and sequenced on an Illumina MiSeq. Coverage of the proband was 99.8%, assessed across the coding exons of the target genes and their intron-exon boundaries (+6 bp and −12 bp) and expressed as the percentage of bases covered at ≥30X. Genetic variants were filtered out if they had a minor allele frequency greater than 2% or if they were outside of the coding exons and their intron/exon boundaries. Next generation sequence analysis (Fig. 2) identified a heterozygous mutation (c.5630A > G, p.(Asn1877Ser)), in the SCN8A gene (Reference sequence: NM_014191.3). Although this variant was not present in the public databases, EVS, 100G and dbSN, two patients with the same SCN8A variant have been described on ClinVar with a phenotype of epilepsy and developmental delay.